REMARKS / ARGUMENTS

Claims 37-57 are currently pending in the application and are directed to compositions comprising antibodies which bind to an osteoprotegerin binding protein (OPGbp) and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

Rejections under 35 U.S.C. 112

Claims 37-57 are rejected under 35 U.S.C. 112, first paragraph, as directed to subject matter which is not enabled by the specification. The grounds for rejection are the alleged failure of the specification to teach the following:

1) How to administer the antibody or fragment thereof or the effective amount necessary to achieve inhibition of bone resorption in a patient; and

2) How to make antibodies against all naturally occurring variants, soluble forms thereof, or fragments thereof of SEQ ID NO: 37 or 39, and how to test specific antibody binding to these form of OPG binding proteins.

Applicant traverses the rejection.

The claimed antibodies are enabled by the teachings of the specification and the knowledge of one skilled in the art.

The test for enablement is whether undue experimentation would be required by one skilled in the art to practice the claimed invention. *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988). Various criteria for determining whether experimentation is undue are set forth in *Wands*. For the reasons set forth below, Applicant asserts that the specification enables the full scope of the claimed invention.

The various OPGbp polypeptides recited in the claims may be made without undue experimentation.

Claim 37 recites compositions comprising antibodies which bind to OPGbp of SEQ ID NO: 37 or 39, naturally occurring variants, soluble forms, or fragments thereof in amounts effective to inhibit bone resorption. Claim 48 recites antibodies raised against those OPGbp polypeptides as immunogens. All the forms of OPGbp in the claims may be made without undue experimentation using the teachings of the specification.

It is not contested that OPGbp of SEQ ID NO: 37 or SEQ ID NO: 39 may be made and used as an immunogen. Soluble forms of OPGbp may be readily prepared using the teachings of the specification: see, for example, p. 14, line 26-p. 15, line 2 which describes the soluble extracellular domain of OPGbp from about residues 70 to 316 in SEQ ID NO: 37 and from about residues 69 to 317 in SEQ ID NO: 39 and N-terminal and C-terminal truncations thereof. Also, Example 6 describes several soluble forms and fragments of OPGbp, from residues 75-316, 95-316, 107-316, 118-316, 128-316, 137-316, 146-316, 156-316, 158-316, 166-316 and 168-316. Soluble OPGbp was shown to be active *in vitro* and *in vivo* in promoting osteoclast formation and bone resorption (see Examples 7 and 8). Naturally occurring variants of OPGbp may be readily identified by one skilled in the art using, for example, hybridization with nucleic acids in either SEQ ID NO: 36 or SEQ ID NO: 38 using procedures such as those described on p. 9, line 19-p. 10, line 9 of the specification. Thus the specification enables those forms of OPGbp which are recited in Claims 37 and 48 (and claims depending therefrom).

The use of the various forms of OPGbp as immunogens to produce antibodies would not require undue experimentation.

It is not contested by the Examiner that OPGbp as in SEQ ID NO: 37 or 39, naturally occurring variants, soluble forms, or fragments thereof, once made, would be immunogenic and would readily produce antibodies when introduced into animals using techniques known in the art. In addition, Applicant has provided in Example 11 methods for producing anti-OPGbp antibodies. Such methods are known in the art to be applicable to a variety of antigens, including those recited in the claims.

Various forms of OPGbp may be used in assays to determine antibody binding without undue experimentation.

OPGbp polypeptides, naturally occurring variants, soluble forms and fragments may be used in enzyme-linked immunosorbent assays (EIA) to screen antibody preparations for binding to a given antigen. Procedures for carrying out such assays are known to one skilled in the art and are also described starting on p. 48, line28 of the specification.

The Examiner alleges that the application fails to describe "any and all osteoprotegerin binding proteins" and that a "large quantity" of experimentation would be required to make all OPGbp variants and test antibody binding to all OPGbp variants. There is no requirement that all species within a claimed genus be enabled but rather that a representative number of a species within the genus be

enabled. *In re Angstadt* 190 USPQ 218 (CCPA, 1976). Based on Applicant's disclosure, it is clear that a representative number of the claimed OPGbp polypeptides have been enabled. In addition, the Examiner has not provided any reasons why a "large quantity" of experimentation would be required to make the claimed OPGbp polypeptides. Even if true, the quantity of experimentation is not a determinant of nonenablement absent any other evidence since the test is whether the experimentation is undue (see *Wands* at 1404). For the reasons set forth above, the specification enables one to practice the claimed invention.

<u>One skilled in the art may readily administer an anti-OPGbp antibody in amounts sufficient to inhibit bone resorption without undue experimentation.</u>

The teachings of the specification, together with the knowledge of one skilled in the art, enable administration of the claimed compositions in amounts sufficient to inhibit bone resorption. For example, various methods of administering the claimed compositions are disclosed on p. 19, lines 20-26. Amounts of an antibody sufficient to inhibit bone resorption may be readily determined by the skilled artisan using an *in vitro* assay as described in Example 8 of the specification or an *in vivo* assay as described in Example 9 of the specification. As further evidence of this, Applicant provides herewith as Exhibit A a Declaration of John K. Sullivan describing anti-OPGbp antibodies which inhibit bone resorption. This declaration was submitted in connection with copending U.S. Serial No. 09/211,315 (the "'315 application") which is the same disclosure as the present application.

The following experimental results are set forth in the declaration:

1) Paragraphs 6 and 7 describe the identification of polyclonal antibodies generated by immunizing rabbits with various OPGbp peptides and polypeptides, such as a BB' loop-Cys peptide, an EF loop6-Cys peptide and human OPGbp[159-317].

2) Paragraph 8 and Attachment No. 1 show binding of the anti-OPGbp antibodies to murine and human OPGbp by EIA.

3) Paragraph 9 and Attachment No. 2 show inhibition of osteoclastogenesis *in vitro* by anti-BB' and anti-human OPGbp[159-317] antibodies.

4) Paragraph 10 and Attachment No. 3 show inhibition of bone resorption and increased bone density *in vivo* by anti-human OPGbp[159-317].

In view of these results, it is clear that administration of antibodies in amounts sufficient to inhibit bone resorption may be readily determined by one skilled in the art.

Applicant respectfully requests withdrawal of the rejection.

It is also argued that Claim 37 fails to recite the property of an antibody which "specifically" binds an OPGbp. The Examiner alleges that an antibody which nonspecifically binds OPGbp would not inhibit bone resorption. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, the claims has been amended to recite an antibody which specifically binds an OPGbp.

Claims 37-57 are rejected under 35 U.S.C. 112, first paragraph, as directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s) has possession of the claimed invention as of the filing date of the application. The Examiner argues that "[w]ith the exception of the antibodies directed to the full length sequences of osteoprotegerin binding protein (SEQ ID NO:37 and SEQ ID NO:39), the skilled artisan cannot envision every detailed chemical structure of the encompassed polypeptides ... ", citing *Fiers v. Revel* (25 USPQ 2d 1601 (Fed. Cir. 1993)), *Fiddes v. Baird* (30 USPQ 2d 1481) and *Amgen v. Chugai Pharmaceuticals* (18 USPQ 2d 1016). Applicants traverse.

The basic inquiry related to written description is whether the Applicant was in possession of the claimed invention *Vas-Cath v. Mahurkar* 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). Possession of the invention may be shown in a number of ways, such as by actual reduction to practice, or by "such descriptive means as words, structures , figures, diagrams, formulas, etc. that fully set forth the claimed invention" *Lockwood v. American Airlines* 41 USPQ2d 1961 (Fed. Cir. 1997).

As discussed above, soluble forms of OPGbp and fragments thereof are described in the specification: see, for example, p. 14, line 26-p. 15, line 2 which describes the soluble extracellular domain of OPGbp from about residues 70 to 316 in SEQ ID NO:37 and from about residues 69 to 317 in SEQ ID NO:39 and N-terminal and C-terminal truncations thereof. Also, Example 6 describes several soluble forms and fragments of OPGbp, from residues 75-316, 95-316, 107-316, 118-316, 128-316, 137-316, 146-316, 156-316, 158-316, 166-316 and 168-316. Thus, Applicant had reduction to practice of the claimed soluble OPGbp polypeptides and fragments thereof. Also, naturally occurring OPG variants are described in the specification at page 15, lines 9-11. In contrast to the facts in *Fiddes* and *Fiers*, the application provides a "representative number" of species within the genus of claimed OPGbp polypeptides and therefore adequately describes the invention.

It is clear to one skilled in the art that Applicant had possession of the claimed OPGbp polypeptides as of the filing date of the application. Withdrawal of the rejection is requested.

Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claim 53 is alleged to be indefinite because the claim does not set forth any steps in the method or process of recombinant DNA expression. It is assumed that the Examiner is referring to Claim 54, which recites recombinant DNA expression, and not Claim 53.

Claim 54 has been amended to clarify the invention by reciting expression of an antibody or fragment in a transformed or transfected host cell. It is believed that the subject matter of Claim 54 is clear to one skilled in the art. Withdrawal of the rejection is requested.

CONCLUSION

Claims 37-57 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: September 12, 2001

Please send all future correspondence to:
U.S. Patent Operations/ RBW
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1789

VERSION WITH MARKINGS TO SHOW CHANGES MADE

37. (amended) A composition comprising an antibody or fragment thereof which specifically binds to an epitope of an osteoprotegerin binding protein and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody or fragment is present in an amount effective to inhibit bone resorption in a mammal [patient], and wherein the osteoprotegerin binding protein comprises the amino acid sequence of Figure 2 (SEQ ID NO:37), Figure 4 (SEQ ID NO:39), a naturally occurring variant thereof, a soluble form thereof, or a fragment thereof.

54. (amended) The composition of Claim 49 wherein the antibody or fragment is produced by [recombinant DNA] expression of a nucleic acid encoding the antibody or fragment in a transformed or transfected host cell.